RECEIVED
CENTRAL FAX CENTER
AUG 25 2006

Appl. No. : 10/063,514
Filed : May 1, 2002

REMARKS

In response to the Office Action dated October 4, 2005, Applicants mailed a Notice of Appeal on December 22, 2005, and an Appeal Brief on February 21, 2006. The Examiner mailed an Examiner's Answer on May 16, 2006. Applicants submitted an RCE and an amendment and response on July 14, 2006. No further Action has been issued. Further to the Office Action mailed October 4, 2005, and in supplement to the submission of July 14, 2006, Applicants submit the following Supplemental Response, which Applicants respectfully request be approved for entry into the record.

Rejection Under 35 U.S.C. §101 – Utility

The PTO has rejected pending Claims 6-7, 9, and 11-17 under 35 U.S.C. § 101 as lacking a specific and substantial asserted utility or a well established utility.

PTO Arguments in rejecting the claims

Applicants understand the PTO to be making two main arguments in response to Applicants' asserted utility:

1. The PTO challenges the reliability of the evidence reported in Example 18, stating that it cannot be determined if the differential PRO874 mRNA expression is "significant or insignificant, relevant or irrelevant, disease-dependent or disease-independent," citing Hu *et al.* (J. Proteome Res. 2003; 2(4):405-12) and LaBaer (Nature Biotechnol. 2003; 21(9):976-7) for support; and

2. The PTO argues that "protein expression levels are not predictable from the mRNA expression levels," citing Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71), Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30) and Allman *et al.* (Blood, (1996) 87(12):5357-68).

Applicants' arguments and rebuttal evidence

Applicants' previous response submitted on July 14, 2006 fully addresses the PTO's first argument regarding the disclosed change in PRO874 transcripts. No further information or remarks are submitted herewith regarding the PTO's first argument.

In addressing the PTO's second argument regarding the relation between differential mRNA levels and protein levels, Applicants have previously addressed the references cited by the PTO. Applicants also previously submitted declarations and scientific publications that support Applicants' position. The details of the teachings of these declarations and references,

and how they support Applicants' asserted utility, are of record and will not be repeated here. In further support of Applicants' assertions that differential mRNA levels generally lead to corresponding differential protein levels, Applicants submit the following Declaration and remarks as a supplement to those submitted in the response mailed July 14, 2006.

Applicants enclose herewith a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 1). Dr. Scott is an independent expert in the field of molecular diagnostics, with over 15 years experience. He is the author of over 40 scientific publications in the fields of protein biology, gene discovery, and cancer, and is an inventor on several issued patents. His curriculum vitae is attached to the declaration. In paragraph 10 of his declaration, Dr. Scott states:

> One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels. *Scott Declaration* at ¶10 (emphasis added).

Applicants submit the opinion of yet another expert in the field that changes in mRNA level for a particular protein in a given tissue generally lead to a corresponding change in the level of the encoded protein. Importantly, Dr. Scott also states that, contrary to the contentions of the PTO, diagnostic markers can be identified "without the need to directly measure individual protein expression levels." This opinion is supported by Dr. Scott's extensive experience in the field, as well as the fact that an entire industry has developed around technology to assess differential mRNA expression. As stated previously, there would be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels.

Applicants submit that the evidence and arguments of record, as supplemented with the Scott declaration and arguments submitted herein establish that it is more likely than not that one of skill in the art would believe that because the PRO874 mRNA is differentially expressed in lung tumors as compared to normal lung tissue, the PRO874 polypeptide will likewise be differentially expressed. This differential expression of the PRO874 polypeptide makes the claimed polypeptides useful as diagnostic tools for cancer, particularly lung cancer.

Appl. No. : **10/063,514**
Filed : **May 1, 2002**

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any necessary fees, including any fees for additional extension of time, or credit overpayment, to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 25, 2006

By: _____
AnneMarie Kaiser
Registration No. 37,649
Attorney of Record
Customer No. 30,313
(619) 235-8550

2870666
082406